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Effect of Methylcellulose on the Nylon Microcapsules Containing Acetaminophen

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Nylon microcapsules containing acetaminophen could be obtained by interfacial polymerization between sebacoyl chloride and 1,6-hexamethylenediamine. Methylcellulose affected the micromeritic properties and dissolution characteristics of microcapsules.

The particle size distribution was affected by the stirring speed and viscosity grade of methylcellulose. The surface observed by the scanning electron microscopy was affected by the methylcellulose.

Nylon microcapsules produced in above method containing acetaminophen exhibited the retarded dissolution in comparison with uncoated acetaminophen.

Release of acetaminophen from microcapsules decreased with decreasing pH of medium and with increasing the viscosity grade of methylcellulose and stirring speed.

Microencapsulation, as a method of protecting or prolonging the release of drugs, has been developed by pharmaceutical scientist for many years. The first patented use of microcapsules was made by Green and Schleicher[1,2] to prepare carbonless copying paper which involves gelatin-acacia coacervation system to entrap emulsified oil droplets containing dissolved dyes.

Luzzi and Gerraughty[3,4] developed a method for the evaluation of drug-containing capsules prepared via complex coacervation.

Miller and Andersen[5] were granted a U.S. patent for the manufacture of microcapsules using "hydrophobic film-forming polymeric wall materials dispersed in a liquid manufacturing vehicles."

And methods have been developed for depositing thin stable semipermeable polymer membrane around aqueous microdroplets. Chang et. al.[6,7] prepared semipe-

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rmeable nylon microcapsules by interfacial polymerization and developed interesting applications of them in physiology. A review by Morgan[8] on interfacial polymerization aids one in understanding the application of this technology to the microencapsulation process. Morgan disclosed that a granular polymer was prepared by adding an organic solution of a diacid chloride to an aqueous solution of a diamine. He also disclosed that in polymerization under agitation a thin film was formed around the periphery of the liquid drop which, when broken, exposes fresh components in the drop to further advance the polymerization reaction. This "thin film formed around the periphery of the liquid drop" is nothing but a microcapsules, and the above procedure corresponds to a microencapsulation process.

Later, Luzzi et. al.[9] used a modification of their technique[6] to encapsulate a water-soluble barbiturate in nylon microcapsules and McGinity[10] developed nylon microcapsules containing formalized gelatin matrix.

Since several different types of nylon can be formed by altering the carbon chain length or the configuration of the amine or diacid, and since each alteration may change the permeability of the resultant film, nylons seem to offer an excellent array of possibilities for the microencapsulation of pharmaceuticals[11].

In this paper, nylon microcapsules containing acetaminophen was prepared with methylcellulose of various viscosity grades. The in vitro dissolution of a acetaminophen from microcapsules, the particle size distribution and the surface characteristics of microcapsules were studied to evaluate the microcapsules.

Experimental

Materials—acetaminophen (K.P.IV), 1,6-hexamethylenediamine(Hayashi pure Chem. Industries), sebacoyl chloride (Tokyo Kasei), methylcellulose(15 cps, Dow Chem.; 400 cps, Carls Erba; 1500 cps, Kanto Chemical Co.), cyclohexane (Wako Pure Chem.), chloroform (Wako Pure Chem.). All materials were of reagent grade purity.

Apparatus—UV spectrophotometer (Pye-Unicam SP 1750), dissolution test unit (Hanson research corp. model No. 72-400-109 attached to Beckman DU 8 spectrophotometer for continuous measurement of absorbance)

Preparation of Microcapsules—The methods of Chang et. al.[6] and Luzzi at. al.[9] with certain modification, were used to prepare nylon microcapsules containing acetaminophen. The basic solutions included: (a) mixed solvent system(consisting of 1 part by volume chloroform and 4 parts by volume cyclohexane); (b) sebacoyl chloride solution (prepared by adding 0.1m*l* of sebacoyl chloride to 25m*l* of the mixed solvent); (c) 1.6-hexamethylenediamine solution (0.4M in 0.45M $NaHCO_3$ buffer of pH 9.8); (d) an aqueous solution consisting of 1w/v% methylcellulose (15, 400, and 1500 cps) and 1w/v% acetaminophen. 2.5m*l* of the 1,6-hexamethylenediamine solution was added to 25m*l* of mixed solvent in a 100m*l* beaker. To this solution, 2.5m*l* of aqueous solution consisting of methylcellulose and acetaminophen was added. The mixed solution was then mechanically stirred with four bladded stirrer for 30 seconds at 720, 860, and 1020 rpm in their respective speed to yield a water-in-oil emulsion. The buffer serves to neutralize hydrogen chloride formed during the polymerization step.[6] Stirring the emulsion, 25m*l* of sebacoyl chloride solution prepared immediately before use was added to the emulsion, and the stirring was continued for 5 minutes to give the nylon-producing reaction. The microcapsules were allowed to settle in the emulsion for 20 minutes and separated from the supernatant. The resultant microcapsules were washed with 25m*l* of mixed solvent and freeze-dried to yield discrete particles.

Particle Size Distribution—Each sample of microcapsules prepared by the above method was placed on an object slide glass and mounted with liquid paraffin. The particle size of microcapsules was determined by a photographic counting method using microscope attached with calibrated micrometer. The particle size was measured along an arbitrarily chosen fixed line. This was termed horizontal diameter by Green.

The geometric mean diameter was calculated from equation as followed:

$$\log G = \frac{1}{n} \sum_i f_i \log d_i$$

where G, geometric mean diameter; n, number of particles observed; f, number of particles in a particle size d; d, particle size.

Not less than 400 particles of each sample were used for the measurement of the diameter.

Assay of Acetaminophen Content and Dissolution—To assay for drug content, the microcapsules were pulverized using a mortar and pestle to fine powd-

er. Each portion of fine powder was weighed accurately and extracted with pH 7.5 phosphate buffer for 20 hours using magnetic stirrer. This extracted solution was filtered and suitably diluted and assayed spectrophotometrically at wave length 248nm.

A 100mg sample of free-flowing microcapsules of size range from 297μm to 500 μm was placed in a basket of dissolution test unit and 900m*l* of liquid (0.1N-HCl, pH 5.0 acetate buffer, dist-water, pH 7.5 phosphate buffer), at 37±0.1°C, was added.

A stirring speed of 50 rpm was used and the dissolved acetaminophen was determined continuously at 248nm.

Scanning Election Microscopy—Dried samples of microcapsules were mounted onto sample stubs with double-sided adhesive tape and were vacuumn coated with gold film approximately 60nm thick. The surface morphology of microcapsules were investigated by a JSM-35 scanning electron microscope (Jeol).

Results and Discussion

Nylon microencapsulation procedure takes advantage of the fact that a polyamide (nylon) membrane forms rapidly at the interface between an aqueous solution of a aliphatic diamine and a solution of dicarboxylic acid halide in an organic solvent[6]. The reaction has been studied in detail by Morgan[8].

The technique of nylon formation by interfacial polymerization is apparently simple, but slight changes in the procedure yield a marked variation in the final product. The viscosity grade of methylcellulose, stirring speed, surfactant, emulsification time, reaction time, and the rate of addition of sebacoyl chloride solution seemed to affect the nature or the formation yield of the microcapsules.

Fig. 1 is photomicrograph of a typical grouping of nylon microcapsules. As in Fig. 1, microcapsules prepared by the methods described above were generally spherical and were not clumped together. Microcapsules containing methylcellulose were denser and more free flowing than microcapsules noncontaining methylcellulose.

Fig. 2 and 3 show the effect of the stirring speed, methylcellulose and drug on the size distribution of microcapsules. Since droplet size in mechanically prepared emulsions was not uniform, the diameter of the microcapsules in any batch

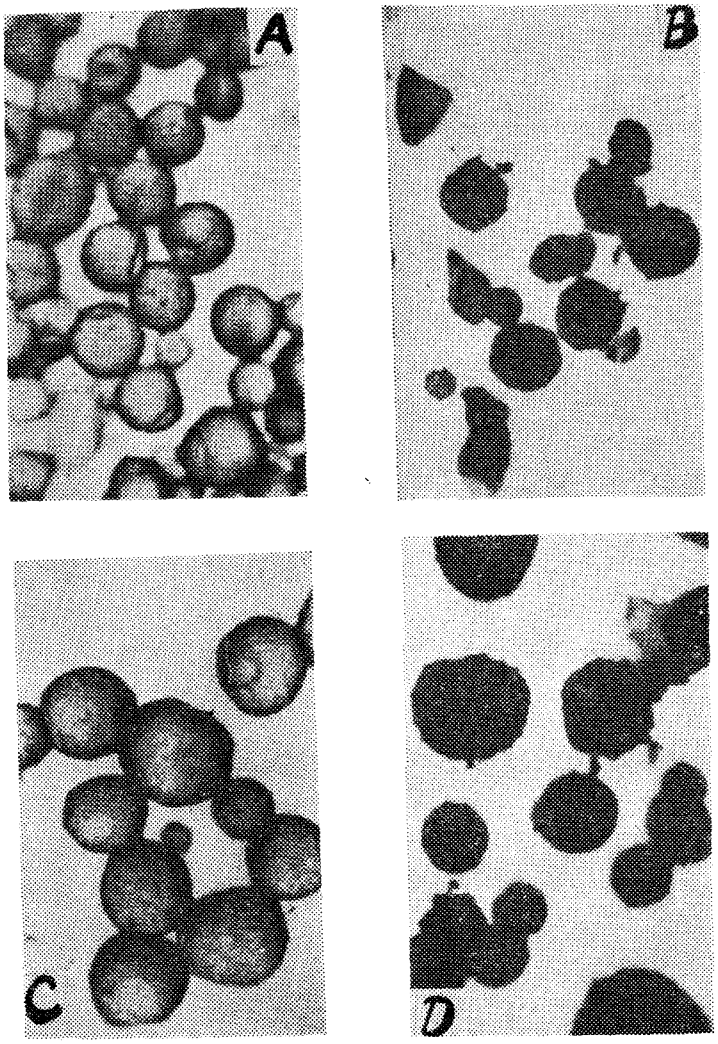

Figure 1—Photomicrographs of nylon microcapsules noncontaining methylcellulose (A,B) and containing methylcellulose of 1500 cps, before(A,C) and after (B,D) drying.

varied over a fairy wide range. With the ingredients and procedures just described, the diameter was strongly affected by the stirring speed and the viscosity grade of methylcellulose. The relationship between diameter of microcapsules and stirring speed was tested without methylcellulose and the relationship between diameter and viscosity grade of methylcellulose was tested by keeping the stirring speed setting at 860 rpm. The size distribution curves clearly became narrower and sharper with increasing the stirring speed and with decreasing the viscosity grade of methylcellulose.

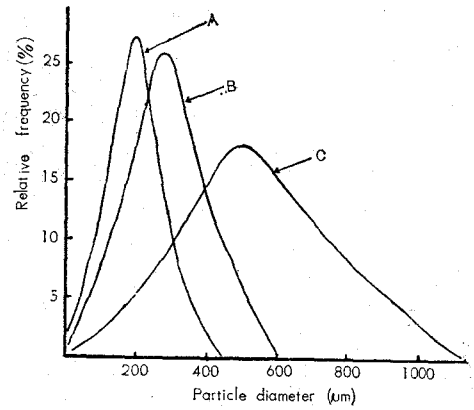

Figure 2—Effect of the stirring speed on the size distribution of nylon microcapsules prepared from 1,6-hexamethylenediamine and sebacoyl chloride in chloroform-cyclohexane (1 : 4).
Key : A, 1020 rpm; B, 860 rpm; C, 720 rpm.

Fig. 4 shows the effect of the viscosity grade of methylcellulose on the dissolution of acetaminophen in pH 7.5 phosphate buffer solution. Acetaminophen contents of microcapsules noncontaining methylcellulose, containing methylcellulose of 15cps, 400 cps, and 1500 cps were 9.4%, 9.3%, and 10.7%, respectively.

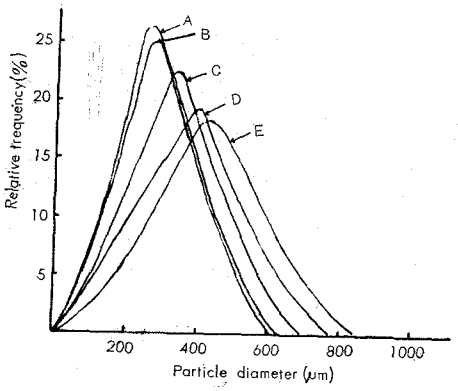

Figure 3—Effect of the viscosity grade of methylcellulose on the size distribution of nylon microcapsules prepared from 1,6-hexamethylenediamine and sebacoyl chloride in chloroform-cyclohexane(1 : 4) at stirring speed 860 rpm
Key : A, microcapsules noncontaining acetaminophen and methylcellulose; B, microcapsules containing acetaminophen only; C, methylcellulose of 15 cps; D, methylcellulose of 400cps; E, methylcellulose of 1500 cps.

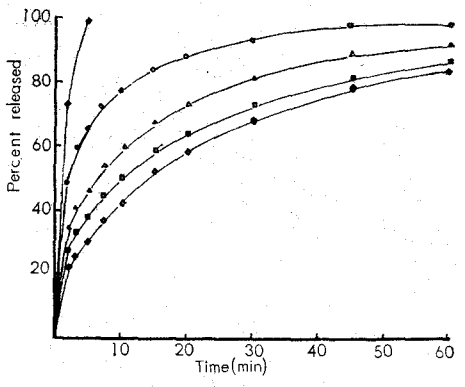

Figure 4—Effect of the viscosity grade of methylcellulose on the dissolution of acetaminophen from nylon microcapsules in pH 7.5 phosphate buffer solution.
Key : ◆ uncoated acetaminophen; ○, microcapsules noncontaining methylcellulose; △, methylcellulose of 15 cps; □ methylcellulose of 400 cps; ◇ methylcellulose of 1500 cps.

Almost 100% of uncoated acetaminophen was dissolved within 5 minutes. Microencapsulated acetaminophen showed the retarded dissolution in comparison with uncoated acctaminophen and as the viscosity grade of methylcellulose increased, the release of drug was retarded. It seemed to be the result of the denser structure (Fig. 8) formed as the viscosity grade of methylcellulose increased.

The mechanism of drug release from nylon microcapsules probably involves leaching of the drug through a network of nylon fibers constituting the microcapsule walls[5,6]. The release of drugs from microcapsules can be treated using the Higuchi equations[12] for diffusional-controlled transport in a polymer matrix. In a homogeneous matrix, the amount of total drug released would be determined by the relationship:

$$Q=[D(2A-C_s)C_st]^{1/2} \quad (1)$$

where Q is the amount of drug released after time t per unit exposed area, D is the diffusitivity of drug in a homogeneous matrix media, A is the total amount of drug present in the matrix per unit volume, and C_s is the solubility of the drug in the matrix substance.

Where matrix is granular and the drug is released by leaching of the penetrating solvent, the following relationship can be seen:

$$Q=[\frac{D\varepsilon}{\tau}(2A-\varepsilon C_s)C_st]^{1/2} \quad (2)$$

where Q is the amount of drug released after time t per unit exposed area, C_s is the solubility and D is the diffusitivity of the drug in the leaching fluid and ε is the porosity and τ is the tortuosity of the matrix.

In the homogeneous case, drug release is directly proportional to the square root of time.

Equation (1) then reduces to:

$$Q=Kt^{1/2} \quad (3)$$

where K is the release rate constant given by:

$$K=[D(2A-C_s)C_s]^{1/2} \quad (4)$$

Equation (3) also describes the case of the granular matrix if the value of K remains constant throughout the leaching process.

Then K is given by:

$$K=[\frac{D\varepsilon}{\tau}(2A-\varepsilon C_s)C_s]^{1/2} \quad (5)$$

The release percent of acetaminophen from nylon microcapsules increased in

Table Ⅰ—Release Rate Constant(K), Correlation Coefficient, and Geometric Mean Diameter for Nylon Microcapsules with Methylcellulose of Various Grades

Viscocity Grade of Methylcellulose	K, $min^{-1/2}$	r	Time Measured, min.	Dg, μm
0*	0.135	0.973	15	283.5
15cps	0.125	0.993	30	317.2
400cps	0.117	0.997	30	355.2
1500cps	0.116	0.998	30	381.7

Kye: K was obtained from the relationship, $Q=Kt^{1/2}$;
r, correlation coefficient;
Dg, geometric mean diameter of dried microcapsules;
*, microcapsules noneontaining methylcellulose.

proportion to the square root of time (Fig. 5). The deviation of release at initial period seemed to be due to the drug retained on the microcapsule wall during the microencapsulation process.

Table Ⅰ shows the release rate constant (K) calculated by linear regression of: $Q=Kt^{1/2}$, correlation coefficient between Q and $t^{1/2}$, and geometric mean diamter of nylon microcapsules with methylcellulose of various viscosity grades.

Fig. 6 shows the effect of pH of medium on the dissolution of acetaminophen from nylon microcapsules with methylcellulose of 1500 cps at stirring speed 860 rpm. The release of acetaminophen showed a tendency to increase at higher pH value. About 79% of the microencapsulated acetaminophen was released to the phosphate buffer and 78%, 76.5%, 70.5% was released to the respective distilled water, acetate buffer, and 0.1N-HCl in 45 minutes.

Table Ⅱ shows the release rate constant (K) and correlation coefficient between Q and $t^{1/2}$ for nylon microcapsules with methylcellulose of 1500 cps in the medium of various pH.

Fig. 7 shows the effect of stirring speed on the dissolution of acetaminophen

Table Ⅱ—Release Rate Constant(K) and Correlation Coefficient for Nylon Microcapsules in the Medium of Various pH

pH of Medium	K, $min^{-1/2}$	r	Time Measured, min.
1.0	0.112	0.999	30
5.0	0.116	0.999	30
7.5	0.116	0.998	30

Key: K was obtained from the relationship, $Q=Kt^{1/2}$;
r, correlation coefficient.

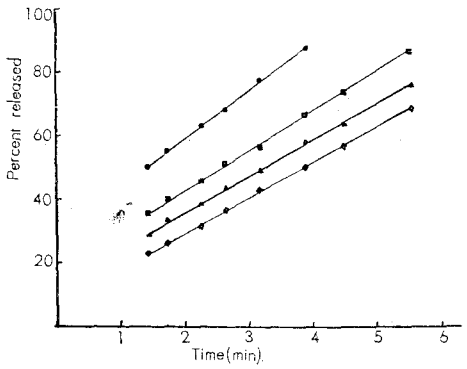

Figure 5—Release(%) of acetaminophen from nylon microcapsules as a function of the square root of time.
Key: ○, microcapsules noncontaining methylcellulose;
□, methylcellulose of 15 cps;
△, methylcellulose of 400 cps;
◇, methylcellulose of 1500 cps.

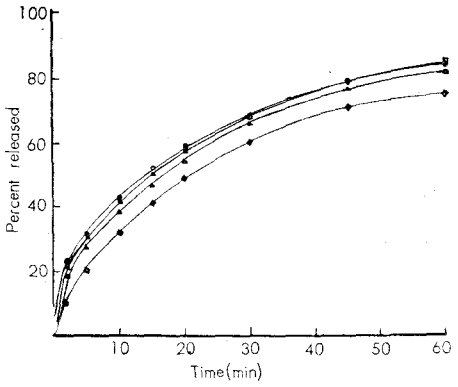

Figure 6—Effect of pH of medium on the dissolution of acetaminophen from nylon microcapsules with methylcellulose of 1500 cps.
Key: ○, pH7.5; □, distilled-water, △, pH 5.0; ◇, pH 1.0.

from nylon microcapsules with methylcellulose of 1500 cps. Release of acetaminophen decreased with increasing the stirring speed. It may be because the stirring speed affects the reaction of 1,6-hexamethylenediamine and sebacoyl chloride[8,13].

Scanning electron micrographs of nylon microcapsules are shown in Fig. 8. The surface appears to be rough and porous with a fibrous structure. These surface photographs do not indicate the inner structural features of the membrane, which

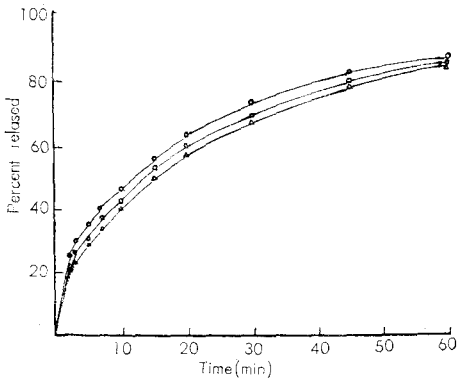

Figure 7—Effect of the stirring speed on the dissolution of acetaminophen from nylon microcapsules with methylcellulose of 1500 cps.
Key: ○, 720 rpm; □, 860 rpm; △, 1020 rpm.

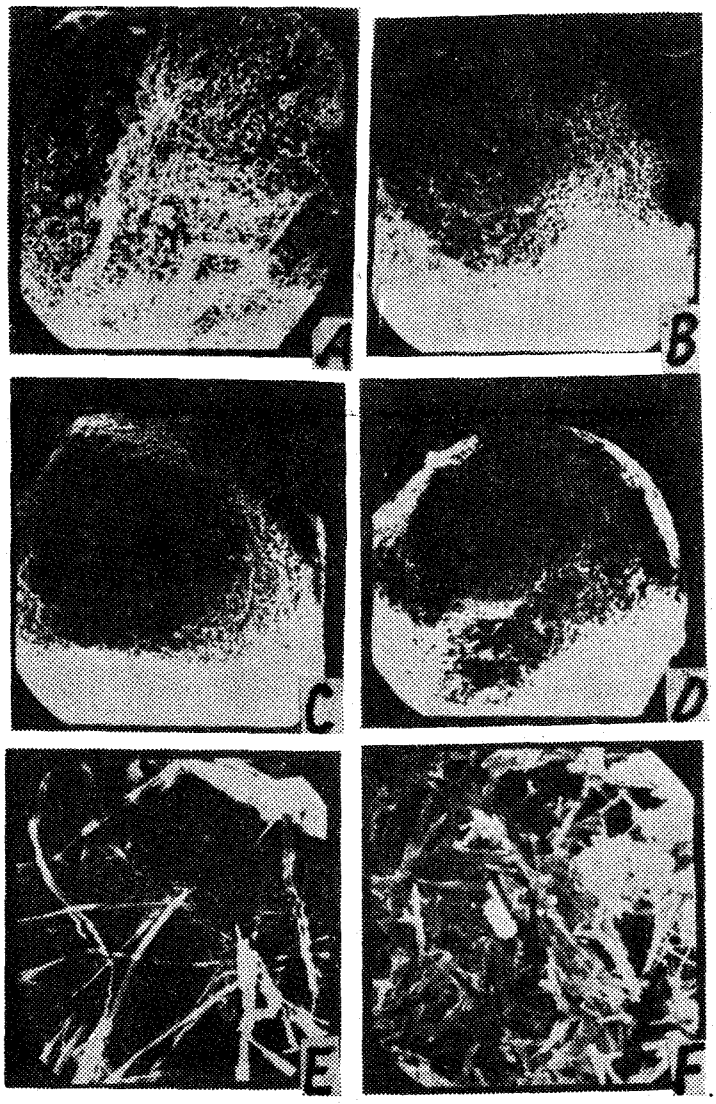

Figure 8—Scanning electron micrographs of dried nylon microcapsules. Key; A, microcapsules noncontaining methylcellulose; B, methylcellulose of 15 cps; C, methylcellulose of 400 cps; D, methylcellulose of 1500 cps; E, enlargement of A; F, enlargement of D. Magnification: A, B, C, D, 200X; E, F, 6000X.

may exhibit different morphology at the matrix interface. The surface of microcapsules noncontaining methylcellulose (Fig. 8 A and E) appears to be very porous in comparison with microcapsules containing methylcellulose of 1500 cps (Fig. 8 D and F).

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